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Research Article

Study Protocol for a Prospective Observational Study to Evaluate the Efficacy of Fosnetupitant for Long-Delayed Chemotherapy-Induced Nausea and Vomiting in Patients Receiving Platinum-Based Chemotherapy (LODEC-N)

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ABSTRACT

Objective: The efficacy of Fosnetupitant (FosNTP) in combination with palonosetron and dexamethasone for preventing highly emetogenic Chemotherapy Induced Nausea and Vomiting (CINV) was demonstrated in a phase III study (CONSOLE study). Although the exploratory analysis of the CONSOLE study suggested the effectiveness of triplet antiemetic therapy, including FosNTP, in the extended overall phase (0 h–168 h), its efficacy in the long-delayed phase (>168 h) has not been evaluated. Additionally, the efficacy of FosNTPs in moderately emetogenic chemotherapy is yet to be elucidated. Therefore, this study aims to prospectively assess the efficacy of FosNTP for CINV in the long-delayed phase (>168 h) in patients receiving platinum-based chemotherapy (cisplatin, carboplatin, and oxaliplatin).

Methods: This is a single-center, single-arm, prospective observational study. Patients scheduled to receive platinum-based chemotherapy will be enrolled. Clinical pharmacists and attending physicians will evaluate all adverse events. The primary endpoint is a long-delayed (120 h–336 h) Complete Control (CC) rate, defined as the proportion of patients experiencing no emetic episodes and moderate or severe nausea without rescue medication. The main secondary endpoints include a long-delayed Complete Response (CR) rate, defined as the proportion of patients experiencing no emesis without rescue medication, and an overall (0 h–336 h) CC, CR, and total control rates, identified as the proportion of patients experiencing no vomiting and nausea without rescue medication in the extended overall phase (0 h–336 h). A subset analysis is planned according to the CINV risk of chemotherapy for each endpoint and time-to-treatment failure for each agent.

Conclusion: This study aims to elucidate the efficacy of triplet antiemetic therapy, including FosNTP, and identify risk factors for CINV in the long-delayed phase in patients receiving platinum-based chemotherapy.

Keywords: Fosnetupitant; Long-delayed CINV; Platinum-based chemotherapy; Oxaliplatin; Cisplatin; Carboplatin; Antiemetics

Abbreviations: FosNTP: Fosnetupitant; PALO: Palonosetron; DEX: Dexamethasone; HEC: Highly Emetogenic Chemotherapy; MEC: Moderately Emetogenic Chemotherapy; CINV: Chemotherapy-Induced Nausea and Vomiting; CC: Complete Control; CR: Complete Response; CTCAE: Common Terminology Criteria for Adverse Events; CYP: Cytochrome *P450*; NK1: Neurokinin-1; RA: Receptor Antagonist; 5-HT3: Serotonin; FosAPR: Fosaprepitant; TC: Total Control

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INTRODUCTION

Chemotherapy-Induced Nausea and Vomiting (CINV) reduces patients' quality of life [1-3], and it has been reported that CINV is among the most severe adverse effects [4-7], and sometimes affects adherence to medication [8-9]. Therefore, controlling CINV is critical for cancer control. To prevent CINV, triplet therapy, including a Neurokinin-1 (NK1) Receptor Antagonist (RA), serotonin (5-HT 3) RA, and Dexamethasone (DEX), has been recommended as the standard treatment for Highly Emetogenic Chemotherapy (HEC) in several guidelines [10-13]. Olanzapine is administered as an additional antiemetic agent because of its effectiveness in treating HEC [14].

Due to antiemetic therapy's development, CINV in the acute phase (0 h–24 h) is frequently controllable. The combination therapy of NK1-RA with Palonosetron (PALO) is preferred for preventing CINV induced by Moderately Emetogenic Chemotherapy (MEC) [15-17], since 5-HT3 RA and PALO have demonstrated favorable results, particularly in the delayed phase (24 h–120 h) [18]. However, because CINV in the delayed phase is unrecognized by medical staff, especially in HEC without cisplatin and MEC, which are frequently performed in outpatient clinics, the control of delayed CINV is overestimated [19]. A few studies have demonstrated that 10%-20% of patients experienced CINV in the delayed phase, even when NK1-RA was administered [15-17,20-22], and that it was often uncontrollable.

Furthermore, in HEC containing cisplatin, some studies on CINV beyond the delayed phase have reported that at least mild nausea was observed more than 60% of patients between cycles 1 and 2 [23], and more than 10% of patients had at least mild nausea on days 14–16 in the first 3 cycles [24]. Therefore, a concern exists that CINV beyond the delayed phase (>120 h) may lead to poor medication adherence and discontinuation of cancer treatment, which affects clinical outcomes [25].

Fosnetupitant (FosNTP) is a new NK1-RA that showed non-inferiority to Fosaprepitant (FosAPR) in combined use of PALO and DEX in patients administrating HEC and was associated with a favorable safety profile compared to FosAPR [26-27]. Currently, FosNTP is added to standard antiemetic therapy for HEC. Because of its long half-life (144 h) [28], and high NK1 receptor occupancy for a long duration [29], FosNTP can be effective for delayed CINV.

Moreover, although network analysis reported no significant additional efficacy of NK1-RA in MEC [30], whether NK1-RA should be added to PALO+DEX remains controversial. In the SENRI trial [15], which investigated the efficacy of NK1-RA added to PALO+DEX in oxaliplatin-based chemotherapy, the addition of NK1-RA showed a favorable antiemetic effect with a difference of more than 10% in the delayed phase in both the Complete Response (CR) (no vomiting and rescue medication use) and the complete protection (no vomiting, rescue medication use, and moderate or worse nausea) rates for 120 h CR and Complete Control (CC) rates. Therefore, the efficacy of NK1-RA in the long-delayed phase can be expected in MEC.

This study aims to assess the effectiveness of triplet antiemetic therapy, including FosNTP, and explore the risk factors for uncontrollable CINV in the long-delayed phase in patients receiving platinum-based (HEC and MEC) chemotherapy.

METHODOLOGY

Study design

This single-center, prospective observational study will be conducted in accordance with the Declaration of Helsinki. The ethical review board of the Institute of Medical Science, University of Tokyo, approved this study's protocol (approval number: 2023-4-0420). This study was registered in the Japan Registry of Clinical Trials (jRCT) as jRCT1030230130. All patients will provide written informed consent.

Participants

The inclusion criteria are as follows: (i) Diagnosis of gastrointestinal or urological cancer; (ii) Planned platinum-based chemotherapy containing triplet therapy (FosNTP+PALO+DEX) as an antiemetic treatment; (iii) Eastern Cooperative Oncology Group performance status of 0–1; (iv) aged>18 years; and (v) Informed consent to participate in this study. The exclusion criteria are as follows: (i) Current use of opioids; (ii) Current use of antiemetic agents (e.g., 5-HT3 RA, NK1-RA, corticosteroid, dopamine receptor antagonist, minor tranquilizer, antihistamine, and benzodiazepine); (iii) brain metastasis with uncontrollable symptoms; (iv) Concurrent radiation therapy to the abdomen/pelvis; (v) Prior platinum-based chemotherapy use within 3 months before enrollment; (vi) Nausea and vomiting within 1 week before enrollment; and (vii) Pregnant and lactating women.

Chemotherapy

MEC and HEC rejimens are included containing cisplatin, carboplatin, or oxaliplatin, such as CapeOX (oxaliplatin 130 mg/m^2, day 1 and capecitabine 1000 mg/m^2 twice daily, days 1–14), SOX (oxaliplatin 130 mg/m^2, day 1 and tegafur/gimeracil/oteracil 80 mg/m^2, days 1–14), and mFOLFOX6 (oxaliplatin 85 mg/m^2; levo-leucovorin 200 mg/m^2; and fluorouracil 400 mg/m^2 bolus and 2400 mg/m^2 46-h continuous infusion, day 1), gemcitabine and cisplatin or carboplatin (gemcitabine 1000 mg/m^2, days 1 and 8 and cisplatin 70 mg/m^2 or carboplatin area under the curve=5, day 1), and ddM-VAC (methotrexate 30 mg/m^2, day 1 and vinblastine 3 mg/m^2, pirarubicin 30 mg/m^2, and cisplatin 70 mg/m^2, day 2). Regarding the mFOLFOX6 and SOX regimens, the addition of molecularly targeted agents or immune checkpoint inhibitors is allowed.

Antiemetic treatment

As an antiemetic therapy for HEC, FosNTP (225 mg/body), PALO (0.75 mg/body), and DEX (6.6 mg/body) are administered intravenously 30 min before chemotherapy on day 1, followed by DEX (8 mg) administered intravenously or orally for 4 days (days 2–5). The same triplet antiemetic therapy will be administered during the DEX period limited to day 1 for MEC (Table 1). Rescue antiemetic agents (metoclopramide, domperidone, alprazolam, and prochlorperazine maleate are recommended as the first choice) will be administered to all participants. The patients will be instructed on how to use rescue medications when they experience severe nausea or vomiting. However, olanzapine will not be administered as a premedication for CINV.

Table 1: Intravenous antiemetic therapy.

Antiemetics		Day 1	Day 2	Day 3	Day 4	Day 5
Cisplatin and Carboplatin	Cisplatin 70 mg/m^2 and Carboplatin AUC 4–5					
Fosnetupitant	IV	235 mg				
Palonosetron	IV	0.75 mg				
Dexamethasone	IV or PO	9.9 mg	6.6 mg (IV) 8 mg (PO)	6.6 mg (IV) 8 mg (PO)	6.6 mg (IV) 8 mg (PO)	6.6 mg (IV) 8 mg (PO)
Oxalipatin	85–130 mg/m^2					
Fosnetupitant	IV	235 mg				
Palonosetron	IV	0.75 mg				
Dexamethasone	IV or PO	6.6 mg				

Note: AUC: Area Under the Curve; IV: intravenous injection; PO: per Os.

Evaluation

CINV will be recorded in a patient's daily diary from 0 h to 336 h after starting the first course of chemotherapy as a self-report of adverse events (Table 2). Patients' symptoms will be recorded in the library, and laboratory data will be assessed at every visit; clinical pharmacists and attending physicians will assess the severity of chemotherapy-related adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Endpoints

The primary endpoint includes the long-delayed (120 h–336 h) CC rate in the first cycle of chemotherapy according to the platinum (cisplatin, carboplatin, and oxaliplatin) administered in the first cycle of chemotherapy. The secondary endpoints are as follows: (i) Long-delayed CR and Total Control (TC) rates; (ii) CC, CR, and TC rates and frequency of mild nausea in the extended overall phase (0 h–336 h); (iii) Risk factors for CINV in patients who do not achieve CC, CR, or TC; (iv) Grade of nausea, vomiting, and anorexia (evaluated using CTCAE version 5.0), and the time of onset of CINV and anorexia in the extended overall phase (0 h–336 h); and (v) The time-to-treatment failure of each agent. The CC rate is defined as the proportion of patients experiencing no emetic episodes and moderate or severe nausea without rescue medication. The CR rate is defined as the proportion of patients experiencing no emesis without rescue medication, and the TC rate is defined as the proportion of patients experiencing no vomiting or nausea without rescue medication. These parameters will be evaluated during the first and second cycles of chemotherapy.

Sample size calculation

No statistical sample size calculations have been conducted because the data analysis for the primary endpoint in this study will be performed using descriptive statistics. Regarding the secondary endpoint, we will use the Kaplan–Meier method and logistic regression analysis to determine the time-to-treatment failure of each agent and the risk factors for CINV, respectively. However, we will not use comparative statistical analysis. The target sample size is 100 participants. The sample size is the number of patients expected to receive chemotherapy for gastrointestinal and urological cancers at our hospital during the study period. We increased the number of participants by an additional 50 to analyze 50 patients, assuming a loss to follow-up. We set more than 50 patient analysis targets according to CONSOLE-BC [27], which evaluates long-delayed CINV, as in this study. However, confounding factors will not be addressed in this study because a comparative analysis will not be performed. Therefore, to control for missing data, a margin of 50 cases will be provided for the number of cases, as is the case for loss to follow-up.

Data collection

The following data will be collected: sex, age, type of cancer, stage, chemotherapy regimen, habitual alcohol consumption (defined as alcohol consumption in excess of social drinking), hyperemesis gravidarum history, motion sickness history, concomitant medication, CINV grade (evaluated using CTCAE version 5.0), and the time of CINV onset. Furthermore, self-reported adverse events (Table 2) will be used to assess nausea and vomiting. CINV will be evaluated based on patient-reported outcomes. The data will be collected between May 2023 and January 2028.

Data analysis

Each evaluation item will be analyzed using descriptive statistics. We will perform multivariate analysis to investigate the risk factors that cause uncontrollable CINV in the delayed phase (120 h–336 h), such as sex, age, habitual alcohol consumption, history of morning sickness during pregnancy, motion sickness history, concomitant use of medications that inhibit cytochrome *P450 (CYP)* 3A4, concomitant use of medications that induce *CYP3A4*, concomitant use of medications metabolized by *CYP3A4*, and cisplatin administration. The time-to-treatment failure for each agent will be determined using the Kaplan–Meier method.

This paper proposed a LODEC-N study protocol to address the effectiveness of triplet antiemetic therapy and explore risk factors for uncontrollable CINV in cancer patients. The results of this study will provide valuable information for cancer patients undergoing platinum-based chemotherapy that is often overlooked in clinical practice.

Table 2: Self-reporting of adverse events.

Side effect self-report			
Name			**Date:**
		Grade	
Nausea	None		
	Mild		
	Moderate		
	Severe		
	Rescue medication use (times)		
	Tolerable (mild nausea and does not need anti-nausea drugs)	1	
	If I use anti-nausea drugs, I can manage to eat.	2	
	I can hardly eat because of nausea.	3	
Vomiting	Vomiting times		
Anorexia	I have a slight loss of appetite.	1	
	I can eat somehow.	2	
	I can hardly eat.	3	
Malaise	I am a little tired; however, it does not interfere with my daily life.	1	
	I frequently lie down.	2	
	I lie down more often than I am awake.	3	
	Bedridden all day long.	4	
Diarrhea	Increased defecation frequency <4 times a day compared to usual.	1	
	Increased defecation frequency 4–6 times a day compared to usual.	2	
	Increased defecation frequency >7 times a day compared to usual.	3	

Note: If you have any other symptoms of concern, please write them down.

DISCUSSION

To realize more precise antiemetic therapy, we believe that elucidating the preventive activity of triplet regimen for HEC and MEC regimens in the extended overall phase (0–336 h) and the risk factors that cause uncontrollable situations are essential. The significance of evaluating the antiemetic effect on both HEC and MEC in this study includes the following: (i) The antiemetic effects of the triplet regimen for HEC in the long-delayed phase are yet to be established; (ii) The antiemetic effects of the triplet regimen on MEC is controversial; and (iii) Because oxaliplatin has a relatively high frequency of CINV among MEC, NK1-RA is necessary; therefore, reports on the efficacy of NK1-RA for oxaliplatin are required. Because the coexistence of multiple anticancer agents hinders accurate evaluation, the antiemetic effect will be evaluated for each agent.

Female sex [31-35], young age [31-32,35-36], little or no previous alcohol use [32,34], history of morning sickness during pregnancy [33], are the risk factors for CINV. The explanatory variables for the multivariate analysis are set as following criteria: Sex; age; drinking history; history of morning sickness during pregnancy; motion sickness history. In addition, concomitant medications were added as explanatory variables as follows, concomitant use of medications that inhibit *CYP3A4*; concomitant use of medications that induce *CYP3A4*; and concomitant use of medications metabolized by *CYP3A4*, a combination of medication that affects the function of *CYP3A4* can affect FosNTP metabolization. Cisplatin administration is also added as explanatory variables, because cisplatin tends to cause delayed CINV.

The pharmacokinetic and pharmacological properties of FosNTP are related to its antiemetic efficacy. NK1-RA has a high long-term occupancy of the NK1 receptor, and its stimulation is related to CINV in the brain. In a pharmacokinetic study of FosNTP, the NK1 receptor occupancy rate was approximately 70% 96 h after administration [29]. Additionally, FosNTPs occupied more than 50% of the NK1 receptor even at 168 h after administration. As mentioned above, FosNTP is expected to demonstrate satisfactory activity in preventing long-delayed CINV. If the efficacy of the triplet regimen (FosNTP+PALO+DEX) in the long-delayed phase are elucidated, this study will provide important information that will enable more detailed explanations to patients. Moreover, identifying the risk factors that cause uncontrollable CINV in the long-delayed phase will enable more appropriate antiemetic therapy for patients with risk factors.

As a method of evaluating CINV, there is a high possibility that the results will differ between prospective and retrospective studies [37-38], and there may also be differences in the evaluation of patients and healthcare professionals, particularly in the delayed phase [19]; therefore, this study is conducted based on the patient-reported and prospective evaluation.

This study has following limitations. First, this is a single-center study and not a comparative study. Second, cancer types are limited to gastrointestinal and urological cancers. Third, because this study is not a randomized trial, improvements in outcomes cannot be compared. Fourth, because we will enroll only platinum-based chemotherapy, we cannot evaluate the preventive effect of other HEC and MEC regimens. Fifth, we will not assess the efficacy of a quartet regimen (including olanzapine) for the HEC regimen [14].

CONCLUSION

Prospective observational study LODEC-N evaluates the efficacy and of triplet antiemetic therapy, including FosNTP, Palo, and DEX. This study will identify risk factors for CINV in the long-delayed phase in cancer patients undergoing platinum-based chemotherapy. Therefore, we will conduct a study to evaluate the quartet regimen for long-delayed CINV in the future.

TRIAL REGISTRATION

This trial was registered in the Japan Registry of Clinical Trials (jRCT) as jRCT1030230130.

TRIAL STATUS

The study is ongoing, and patients are currently being enrolled. Enrollment will begin in May 2023. As of May 2023, 30 of the patients have participated. Thus, we expect to complete the recruitment by January 2028.

DECLARATION

Ethics approval and consent to participate

The study protocol will be performed in accordance with the Declaration of Helsinki and approved by the ethical review board of The Institute of Medical Science, the University of Tokyo (approval number:2023-4-0420). This study was registered in the Japan Registry of Clinical Trials (jRCT) as jRCT1030230130. All patients will provide written informed consent.

INFORMED CONSENT STATEMENT

All patients are required to provide written informed consent.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Data supporting the findings of this study are available from the corresponding author, YI, upon reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

Iimura Y wrote the main manuscript and prepared Tables 1–2. Iimura Y conceived the idea presented in this study. Kuroda S and Iihara H revised the study design. All authors reviewed the manuscript.

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